

Supplementary appendix

Supplementary Table I. Initial VTE presentation.

	Active brain cancer	Active non-brain cancer	Non-active or no cancer
In patients with PE, N	318	8,428	43,568
Dyspnea	246 (79%)	6,729 (81%)	34,642 (81%)
Chest pain	128 (41%)	2,886 (35%)*	19,937 (47%)*
Hemoptysis	10 (3.3%)	366 (4.5%)	2,301 (5.5%)
Syncope	38 (12%)	903 (11%)	6,329 (15%)
SBP levels <90 mm Hg	17 (5.3%)	334 (4.0%)	1,355 (3.1%)*
SBP levels <100 mm Hg	37 (12%)	788 (9.4%)	3,244 (7.4%)†
Heart rate ≥100 bpm	149 (49%)	3,264 (40%)†	14,599 (35%)‡
Sat O ₂ levels (mean %±SD)	92±8	92±7	92±7
Sat O ₂ levels <90% (n=29,295)	38 (23%)	1,252 (29%)	6,968 (28%)
In patients with isolated lower-limb DVT, N	286	6,761	34,953
Proximal DVT	241 (39%)	5,750 (85%)	28,160 (35%)*
Bilateral DVT	19 (3.1%)	481 (7.1%)	887 (1.1%)‡
In patients with isolated upper-limb DVT, N	12	1,618	2,433
Catheter-related	9 (75%)	1,095 (69%)	819 (35%)†

Comparisons between patients with brain cancer vs. other subgroups: *p <0.05; †p<0.01; ‡p <0.001

Abbreviations: PE, pulmonary embolism; DVT, deep vein thrombosis; SBP, systolic blood pressure; SD, standard deviation.

Supplementary Table II. Main features and management of patients who experienced intracranial bleeding

	Active brain cancer	Active non brain cancer	Non-active or no cancer
Patients, N	17	58	153
Age (mean years±SD)	58±14	67±13*	74±12‡
Male gender, N (%)	13 (76%)	34 (59%)	68 (44%)*
Additional VTE risk factors,			
Postoperative, N (%)	9 (53%)	5 (8.6%)†	18 (12%)‡
<30 days before, N (%)	7 (41%)	5 (8.6%)†	15 (9.8%)†
30-60 days before, N (%)	2 (12%)	0	2 (1.3%)
Immobility ≥4 days, N (%)	3 (18%)	11 (19%)	55 (36%)
Initial VTE presentation,			
Lower Limb isolated DVT, N (%)	4 (24%)	27 (43%)	47 (31%)
Pulmonary embolism, N (%)	13 (76%)	25 (43%)†	106 (69%)
Upper Limb isolated DVT, N (%)	0	6 (14%)	0
Duration of therapy until bleeding,			
Mean days (±SD)	40±28	32±25*	29±26
Median days (IQR)	29 (12-69)	28 (10-47)*	20 (7-52)
Ongoing therapy at bleeding,			
Unfractionated heparin, N (%)	1 (5.9%)	2 (3.4%)	11 (7.2%)
LMWH, recommended doses*, N (%)	6 (35%)	33 (57%)	48 (31%)
LMWH, higher doses, N (%)	0	1 (1.7%)	3 (2.0%)
LMWH, lower doses, N (%)	7 (41%)	14 (24%)	16 (10%)†
Fondaparinux, recommended doses**, N (%)	0	1 (1.7%)	1 (0.6%)
Fondaparinux, higher doses, N (%)	0	0	1 (0.6%)
Fondaparinux, lower doses, N (%)	0	0	1 (0.6%)
Rivaroxaban, recommended doses, N (%)	1 (5.9%)	1 (1.7%)	4 (2.6%)
Rivaroxaban, lower doses, N (%)	0	0	1 (0.6%)
Apixaban, recommended doses, N (%)	1 (5.9%)	1 (1.7%)	0
Apixaban, lower doses, N (%)	0	0	0
Edoxaban, recommended doses, N (%)	0	0	1 (0.6%)
Edoxaban, lower doses, N (%)	0	0	0
Dabigatran, N (%)	0	1 (1.7%)	0
Thrombolytics, N (%)	0	0	6 (3.9%)
Vitamin K antagonists	1 (5.9%)	2 (3.4%)	57 (37%)*
Other drugs	0	2 (3.4%)	2 (3.4%)
Inferior vena cava filter, N (%)	4 (24%)	12 (21%)	43 (28%)
Management of intracranial bleeding,			
PCC, N (%)	0	0	7 (8.5%)
Fresh frozen plasma, N (%)	1 (5.3%)	0	6 (7.8%)
Surgery, N (%)	1 (5.3%)	2 (8.3%)	5 (9.8%)
Embolectomy N (%)	0	1 (1.7%)	1 (2.0%)
Concomitant drugs,			
Antiplatelets, N (%)	3 (17%)	11 (21%)	37 (27%)
NSAIDs, N (%)	2 (11%)	4 (7.7%)	11 (8.0%)
Chemotherapy, N (%)	8 (44%)	28 (53%)	0
Radiotherapy, N (%)	6 (33%)	8 (16%)	0
Death within 30 days after intracranial bleeding,			
Yes	6 (32%)	28 (48%)	38 (25%)

<i>Causes of death,</i>			
Intracranial bleeding, N (%)	6 (32%)	24 (41%)	33 (22%)
Disseminated cancer, N (%)	0	3 (5.2%)	0
Respiratory insufficiency, N (%)	0	0	1 (0.7%)
Other	0	1 (1.7%)	4 (2.6%)

Comparisons between patients with brain cancer vs. other subgroups: *p <0.05; †p<0.01; ‡p <0.001

Abbreviations: SD, standard deviation; VTE, venous thromboembolism; DVT, deep vein thrombosis; IQR, inter-quartile range; LMWH, low-molecular-weight heparin; NSAIDs, non-steroidal anti-inflammatory drugs.

Supplementary Table III. Main features and 90-day outcome of patients, according to treatment with standard therapy or direct oral anticoagulants.

	Active brain cancer		Active non brain cancer		Non-active or no cancer	
	DOACs	Other	DOACs	Other	DOACs	Other
Day 0 to Day 10						
Patients, N	2	611	208	16,500	3,464	77,274
Age (mean years±SD)	43±35 [‡]	61±13	67±14	68±13	59±18 [‡]	65±14
Male gender, N (%)	1 (50%)	367 (60%)	103 (49%)	8,658 (52%)	1,886 (54%) [‡]	37,728 (49%)
Initial VTE presentation,						
Lower limb isolated DVT, N (%)	0	284 (97%)	84 (85%)	6,630 (87%)	1,668 (95%) [*]	33,183 (96%)
Pulmonary embolism, N (%)	2 (100%)	315 (52%)	111 (53%)	8,274 (50%)	1,699 (49%) [‡]	41,767 (54%)
Upper limb isolated DVT, N (%)	0	12 (2.6%)	16 (11%)	1,593 (14%)	99 (4.2%)	2,322 (4.4%)
Outcomes,						
Major bleeding	0	3 (0.5%)	1 (0.5%)	208 (1.3%)	11 (0.3%) [‡]	622 (0.8%)
<i>Site of major bleeding,</i>						
Gastrointestinal	0	1 (0.2%)	1 (0.5%)	95 (0.6%)	180 (0.2%)	3 (0.1%)
Cerebral	0	2 (0.3%)	0	16 (0.1%)	96 (0.1%)	2 (0.06%)
Haematoma	0	0	0	27 (0.2%)	175 (0.2%) [†]	0
Recurrent VTE	0	11 (1.8%)	0	110 (0.7%)	620 (0.8%) [*]	17 (0.5%)
Recurrent PE	0	10 (1.6%)	0	67 (0.4%)	269 (0.3%)	6 (0.2%)
Recurrent DVT	0	1 (0.2%)	0	46 (0.3%)	352 (0.5%)	11 (0.3%)
Death	0	16 (2.6%)	2 (0.9%) [*]	677 (4.1%)	1,742 (2.3%) [‡]	20 (0.6%)
Day 11 to Day 90						
Patients, N	12	575	811	14,584	12,224	67,029
Age (mean years±SD)	49±18 [‡]	61±13	69±12 [‡]	67±13	62±18 [‡]	65±18
Male gender, N (%)	8 (67%)	346 (60%)	386 (48%) [†]	7,774 (53%) [†]	6,411 (52%) [‡]	32,544 (49%)
Initial VTE presentation,						
Lower limb isolated DVT, N (%)	2 (100%)	272 (97%)	284 (84%)	6,074 (86%)	4,481 (94%) [‡]	30,035 (96%)
Pulmonary embolism, N (%)	10 (83%) [*]	291 (51%)	464 (57%) [‡]	7,217 (49%)	7,435 (61%) [‡]	34,909 (52%)
Upper limb isolated DVT, N (%)	0	12 (2.8%)	62 (12%)	1,494 (14%)	309 (4.0%)	2,085 (4.5%)
Outcomes,						
Major bleeding	3 (25%) [†]	16 (2.8%)	22 (2.7%)	284 (1.9%)	46 (0.4%) [‡]	520 (0.8%)
<i>Site of major bleeding,</i>						
Gastrointestinal	1 (8.3%) [*]	1 (0.2%)	11 (1.4%)	146 (1.0%)	19 (0.2%)	154 (0.2%)
Cerebral	2 (17%) [*]	13 (2.3%)	3 (0.4%)	30 (0.2%)	5 (0.04%) [*]	84 (0.1%)
Haematoma	0	2 (0.3%)	0	24 (0.2%)	7 (0.06%) [‡]	144 (0.2%)
Recurrent VTE	0	12 (2.1%)	10 (1.2%) [†]	432 (2.9%) [†]	56 (0.5%) [‡]	565 (0.8%)
Recurrent PE	0	5 (0.9%)	5 (0.6%)	201 (1.4%)	26 (0.2%) [*]	237 (0.3%)
Recurrent DVT	0	7 (1.2%)	6 (0.7%) [*]	243 (1.6%)	30 (0.2%) [‡]	329 (0.5%)
Death	2 (17%)	82 (14%)	46 (5.7%) [‡]	2,295 (16%)	97 (0.8%) [‡]	1,376 (2.1%)

Comparisons between patients with DOACs vs. other drugs: *p <0.05; †p<0.01; ‡p <0.001

Abbreviations: DOACs, direct oral anticoagulants; SD, standard deviation; VTE, venous thromboembolism;

DVT, deep vein thrombosis; PE, pulmonary embolism.

Supplementary Table IV. Multivariable analyses using competing risk models for VTE recurrences, major bleeding or intracranial bleeding within the first 90 days, including recommended/not recommended doses of drugs. Results expressed as hazard ratio and 95% confidence intervals. Patients receiving unfractionated heparin, vitamin K antagonists or thrombolytics are not included in these analyses since they may be not classified as receiving appropriate/higher/lower doses.

	Intracranial bleeding	Major bleeding	VTE recurrences
Clinical characteristics,			
Male gender	1.55 (1.03-2.34)*	0.90 (0.78-1.05)	1.15 (0.99-1.35)*
Age >70 years	-	1.17 (0.85-1.41)	0.68 (0.57-0.82)‡
Body weight < 75 kg	1.60 (0.99-2.52)	0.93 (0.78-1.09)	-
Underlying conditions,			
Chronic lung disease	-	1.18 (0.95-1.47)	-
Chronic heart failure	-	1.35 (1.04-1.76)*	-
Atrial fibrillation	-	1.06 (0.81-1.40)	-
Recent (<30 days) major bleeding	4.07 (2.16-7.67)‡	3.10 (2.34-3.86)‡	1.70 (1.18-2.45)†
Prior VTE	-	0.88 (0.69-1.11)	1.54 (1.26-1.89)‡
Blood tests,			
Anaemia	0.95 (0.60-1.50)	1.90 (1.60-2.23)‡	1.03 (0.86-1.22)
Leukocyte count >11,000/uL	-	1.47 (1.26-1.72)‡	1.49 (1.26-1.76)‡
Platelet count <100,000/uL	3.44 (1.89-6.27)‡	2.12 (1.59-2.83)‡	1.70 (1.23-2.35)†
Platelet count >450,000/uL	-	1.49 (1.15-1.95)†	1.23 (0.90-1.69)
CrCl levels <60 mL/min	1.65 (1.07-2.55)*	2.03 (1.68-2.44)‡	-
Concomitant drugs,			
Antiplatelets	0.51 (0.32-0.82)*	0.95 (0.78-1.16)	-
Corticosteroids	0.86 (0.49-1.50)	1.23 (0.99-1.51)	1.03 (0.81-1.30)
NSAIDs	-	-	1.27 (0.95-1.69)
Psychotropics	-	-	0.71 (0.55-0.92)†
Initial VTE presentation,			
Lower limb isolated DVT	Ref.	Ref.	Ref.
Pulmonary embolism	-	1.16 (0.99-1.35)	0.74 (0.62-0.86)‡
Upper limb isolated DVT	-	-	0.70 (0.51-0.95)*
Study subgroups,			
No cancer	Ref.	Ref.	Ref.
Active brain cancer	19.7 (10.4-37.6)‡	2.77 (1.69-4.54)‡	2.61 (1.52-4.51)†
Active non-brain cancer	1.80 (1.12-2.91)*	1.62 (1.38-1.90)‡	2.84 (2.39-3.38)‡
Intensity of anticoagulation,			
Recommended doses	Ref.	Ref.	Ref.
Lower doses	-	0.71 (0.61-0.84)‡	0.90 (0.76-1.06)
Higher doses	-	0.85 (0.64-1.12)	0.57 (0.40-0.83)†

*p <0.05; †p<0.01; ‡p <0.001

Abbreviations: VTE, venous thromboembolism; CrCl, creatinine clearance; DVT, deep vein thrombosis; NSAIDs, nonsteroidal anti-inflammatory drugs; Ref., reference.

Supplementary Table V. Treatment strategies and Clinical outcomes within the first 3 months of anticoagulant therapy by type of brain tumor.

	Glioblastoma	Other malignant brain cancers	Benign brain tumors
Patients, N	256	137	127
Initial therapy,			
Unfractionated heparin	11 (4.3%)	8 (5.8%)	8 (6.3%)
LMWH, recommended doses	163 (71%)	93 (74%)	80 (74%)
LMWH, higher doses	4 (1.6%)	5 (3.6%)	5 (4.6%)
LMWH, lower doses	64 (28%)	27 (22%)	23 (21%)
Fondaparinux, recommended doses	5 (2.0%)	0	3 (2.4%)
Rivaroxaban, recommended doses	0	1 (0.7%)	1 (0.8%)
Apixaban, recommended doses	1 (0.4%)	0	0
Apixaban, lower doses	0	1 (0.73%)	0
Thrombolytics	1 (0.4%)	0	3 (2.4%)
Inferior vena cava filter	24 (9.4%)	19 (14%)	17 (13%)
Long-term therapy,			
Vitamin K antagonists	16 (6.3%)	27 (20%) [‡]	51 (40%) [‡]
LMWH, recommended doses	134 (52%)	59 (43%)	44 (40%)
LMWH, higher doses	0	2 (1.5%)	2 (1.6%)
LMWH, lower doses	88 (34%)	31 (22%)	20 (16%)
Rivaroxaban, recommended doses	1 (0.4%)	5 (3.6%) [*]	2(1.6%)
Rivaroxaban, higher doses	0	0	1 (0.8%)
Apixaban, recommended doses	2 (0.8%)	5 (3.6%)	1 (0.8%)
Fondaparinux, recommended doses		1 (0.73%)	0
90-day outcomes,			
Major bleeding	12 (4.7%)	4 (2.9%)	5 (3.9%)
<i>Site of major bleeding,</i>			
Gastrointestinal	0	1 (1.5%)	2 (1.6%)
Cerebral	10 (3.9%)	3 (2.2%)	2 (1.6%)
Genitourinary	0	0	0
Retroperitoneal	0	0	0
Haematoma	2 (0.8%)	0	1 (0.8%)
Recurrent VTE	10 (3.9%)	4 (2.9%)	1 (0.8%)
Recurrent PE	6 (2.3%)	2 (1.5%)	0
Recurrent DVT	4 (1.6%)	2 (1.5%)	1 (0.8%)
Death	49 (19%)	18 (13%)	7 (5.5%) [‡]
<i>Causes of death,</i>			
Pulmonary embolism	0	1 (0.73%)	1 (0.8%)
Bleeding	5 (2.0%)	2 (1.5%)	2 (1.6%)
Intracranial bleeding	5 (2.0%)	1 (0.73%)	1 (0.8%)
Cancer	37 (14%)	10 (7.3%) [*]	1 (0.8%) [‡]
Sudden, unexpected	1 (0.4%)	0	0
Respiratory insufficiency	0	1 (0.73%)	0

*p <0.05; [†]p<0.01; [‡]p <0.001

APPENDIX

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